Prevalence and Outcome of Lung Cancer in Lung Transplant Recipients

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Glossary of abbreviations:

IPF: Interstitial Pulmonary Fibrosis, COPD: Chronic Obstructive Pulmonary Disease, NYHA: New York Heart Association, FEV: Forced Expiratory Volume, DLCO: diffusing capacity of lung for carbon monoxide, LAS: Lung Allocation Score, CNI: Calcineurin inhibitors

Section 1: Introduction

Lung transplantation provides a life-saving therapy for patients with end-stage pulmonary disease. Two of the three most common indications for lung transplantation include idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD). After these two disease processes comes cystic fibrosis, as the third most common indication for lung transplantation in both adult and pediatric patient populations. In all three disease states, oxygenation of blood can decrease and cause symptomatic end stage lung disease and an oxygen requirement in patients. Patients begin to be considered for lung transplantation when life expectancy is not predicted to exceed 24-36 months despite optimal and maximal medical management and they have class III or IV New York Heart Association (NYHA) symptoms. Specifically for patients with COPD, FEV1 can help determine when a patient should be referred for transplant. FEV1 of less than 30% predicted is associated with a 60-80% two year survival rate, and hence, transplation should be offered to COPD patients with an FEV1 substantially less than 30% predicted. In patients with idiopathic pulmonary fibrosis, the diffusing capacity of lung for carbon monoxide (DLCO) is a parameter that is useful in predicting the survival of patients with restrictive disease; a DLCO of less than 35-39% is associated with a higher risk of mortality. In the era of the Lung Allocation Score (LAS), transplantation for fibrotic lung disease is becoming more common. In 2009 more than 3,200 lung transplantation were performed worldwide in accordance with the LAS. The LAS is used to prioritize waiting list candidates based on a combination of waitlist urgency and post-transplant survival. Waitlist urgency is defined as what is expected to happen to a candidate, given his or her characteristics, in the next year if he or she doesn't receive a transplant. Post-transplant survival represents what is expected to happen to a candidate, given his or her characteristics, in the first year after a transplant if he or she does receive the transplant. Lung transplant outcomes have greatly improved since the first lung transplant in 1983 [1], but significant morbidity still results from long-term immunosuppressive therapy needed to prevent graft rejection. Currently the national average 1 month graft survival rate is >95%, with a 1 year average of 83%, and 3 year average of 64%. Immunosuppression reduces the natural antitumor immune response, predisposing transplant recipients to an increased risk for malignancies [2]. At least one malignancy is diagnosed in 13% of 5-year survivors and in 28% of 10-year survivors. There is compelling evidence to support the

notion that immunogenic tumors, in murine models and cancer patients, can be rejected by the immune system under optimum conditions for activating adaptive and nonadaptive antitumor immune responses. In the last decade, there has been an increase in the development of lung cancer in lung transplant recipients [3]. This increase may be due to a longer survival time for transplant recipients [4] and an increased number of patients receiving transplants for COPD and IPF [3] at an older age. Twenty percent of lung transplants performed since 2001 have been in recipients older than 59. In the general population, crossing the age of 60 years doubles the risk for lung cancer. In addition, compared to transplants performed between 1989-1996, during which there was a 40% survival rate at 5 years post-transplant, survival for lung transplant recipients at a 5 year time point increased to 60% for patients who received transplants between 1997-2007. A review of the Scientific Registry of Transplant Recipients found an elevated standardized incidence ratio of 6.13 for the development of lung cancer in lung transplant recipients, higher than any other solid organ recipient cohort [5]. The overall cancer risk among 175,732 solid organ recipients was 10,656 cases. The most common malignancy with elevated risk was non-Hodgkin lymphoma. After lung transplant recipients, kidney, liver, and heart transplant recipients had the greatest risk for diverse infection-related and unrelated cancers. The higher incidence of lung cancer in lung transplant recipients may be partially explained by the fact that COPD and IPF, both conditions with a high prevalence of smokers are some of the most common indications for lung transplant. There is an increased risk of lung cancer in COPD, and whether obstructive lung disease itself is an independent risk factor for lung cancer is subject to debate [6]. Further, IPF has been linked to an increased risk for the development of lung cancer, 17% in one autopsy series [7]. This reflects a greater prevalence than in patients without IPF and seems to persist even when smoking habits are considered [8]. Finally and importantly, immunosuppressive regimens in lung transplant are substantially more aggressive than in other solid organ transplant, since the incidence of acute and chronic organ rejection is markedly higher, representing an important risk factor for development of malignancy post-transplant, through different mechanisms [9-13]. Immunosuppresive drugs also may act directly on carcinogenic pathways. Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, may enhance tumor progression by inhibition of DNA repair, antiapoptotic effect in damaged cells, and inhibition of cell adhesion favoring cell migration and metastatic spread. In addition, azathioprine may promote microsatellite DNA instability. Newer agents, such as mycophenolate

and mTOR inhibitors demonstrate the ability to reduce tumor progression. Patient's undergoing unilateral lung transplants are placed at higher risks for malignancy as the remaining lung, formerly exposed to inhaled risk factors, is not introduced to the stress of immunosuppression.

While the increased risk for cancer post-lung transplant has been documented, there are only a few studies presenting data detailing the discovery of bronchogenic carcinoma in the explanted lung at the time of surgery [14-16]. One study reported 2 cases of stage I adenocarcinoma, both less than 1 cm, incidentally found in the pneumonectomy specimen at the time of single lung transplantation. The remainder of each lung showed no evidence of adenocarcinoma and all lymph nodes were negative. Work-ups for an occult malignancy before and after surgery were negative in both cases. Further reports include a recommended work-up after the discovery of the incidental lung cancer, involving mediastinal staging with mediastinoscopy, with the back thought of potential adjuvant therapy. Tapering immunosuppression during the initial post transplant period was not addressed. Such reports indicate a 5-year survival rate for patients with cancer in the explanted lung ranging from 25-51%, depending on pTNM stage. Survival thus far appears to be more favorable fore patients with stage I disease (51% at 5 years) compared with stages II and III (14%). The majority of patients with stage II or III carcinoma experienced recurrence and died within the first year of transplantation.

A better understanding of the prevalence of lung cancer and the definition of at-risk populations in patients under going lung transplantation could help to identify methods to improve transplant safety and the prognoses for patients who develop bronchogenic carcinoma. It is unclear whether certain chemotherapy or immunosuppression regimens can best decrease tumor burden and the risk for metastatic disease in such patients. In addition, it is unclear who the patients are who are harboring lung cancers incidentally found on pathology reviews from lung transplantations. To this end, we conducted a retrospective study on both the discovery of lung cancer in explanted lungs and the development of de novo bronchogenic carcinoma post-transplant at Brigham and Women's Hospital.

Section 2: Methods

We conducted a retrospective chart review of all patients who underwent a lung transplant at Brigham and Women's Hospital (BWH) between January 1990 and June 2012. The study was reviewed and approved by BWH institutional review board (Protocol Number 2011-P-002392/1).

In the study period a total of 457 subjects underwent lung transplant at BWH. Of these subjects, 5 received a retransplant of an already transplanted lung, bringing the total number of lung transplant surgeries to 462. In these 5 cases, native lungs were counted as explants. Transplanted lungs were counted both as a transplant and explants. 4 patients were transplanted for chronic rejection and one patient was retransplanted for recurrent acute rejection.

Lung transplant recipients in whom cancer was identified in the explanted lung at the time of transplant, or in whom lung cancer was identified post-transplant either in the native lung or in the allograft, were identified from Brigham and Women's Hospital's computerized hospital records and lung transplant surgery database. Histology slides from all identified cases of malignancy were reviewed by a pulmonary pathologist (RP) to confirm the cancer diagnosis. Cases of post-transplant lymphoproliferative disorder were excluded from the post transplant lung cancer analysis.

During the study period, the policy at BWH required all patients listed for lung transplantation to keep computed tomography (CT) scans of the chest updated yearly prior to lung transplant. Suspicious findings on these scans were evaluated according to published guidelines [17], and any malignant findings seen on a biopsy, or a positive fludeoxyglucose positron emission tomography (FDG-PET) when biopsies are deemed unsafe because of the patient's respiratory compromise resulted in the removal of the subject from the lung transplant eligibility list. Of the patients who were found to have carcinoma in the explanted lung, only one was transplanted prior to the policy of yearly CT scans. The CT scan in this case was performed 21 months prior to transplant and had not shown any evidence of malignancy.

Donors with a greater than 20 pack year history of smoking were screened with chest CT scan prior to organ acceptance. Evidence of suspicious nodules on donor imaging or gross inspection

at the time of procurement led to either biopsy with frozen section analysis and/or exclusion from lung donation.

Post-transplant, subjects received immunosuppression consisting of standard therapy at the time of transplant. In 2001 our program transitioned from cyclosporine A to tacrolimus (levels adjusted to 8-12 ng/ml in the first year post-transplant, and 6-8 ng/ml thereafter), and from azathioprine to mycophenolate (1 gm twice a day), as standard de novo immune suppression. In 2008, our program substantially decreased the systemic corticosteroid dosing administered to recipients, and transitioned from equine antithymocyte globulin (ATG) to Rabbit ATG for induction. Most patients receive induction unless there is a concern for significant infectious risk.

Per standard pathology protocol at our institution, lungs explanted at the time of transplantation were inflated with formalin through the bronchus for adequate fixation. The lungs were serially sectioned thinly in either a coronal or parasaggital plane to evaluate the parenchyma for pathologic processes such as the underlying lung disease, infection or malignancy. Several histological sections from the central and peripheral aspects of each lobe were taken, in addition to sections of any masses, nodules, cysts or areas of consolidation. Standard sections of the bronchial and vascular resection margins as well as samples of hilar and intrapulmonary lymph nodes were taken.

In addition, and depending on their clinical status, subjects underwent serial surveillance bronchoscopies at 1 week and 1, 3, 6, and 12 months post-transplant, with transbronchial biopsies taken at 1, 3, 6, and 12 months to evaluate for acute allograft rejection.

Statistical analysis

Results are expressed as mean SD of the mean unless otherwise specified. A t-test was performed to calculate difference in means. A Chi square test was performed to calculate difference of proportion. Statistical analysis was performed using Graphpad Prism (GraphPad Software Inc, La Jolla, CA). A $p < 0.05$ was used as the cutoff to determine statistical significance.

Section 3: Results

The mean age of the recipients was 49.13 years. Of the 462 cases, 214 were bilateral lung transplants. The three most common causes for lung transplantation were COPD, IPF, and CF (Table 1). Twenty three percent of subjects with IPF and 10% of subjects with COPD received bilateral transplants. Recipients of lung transplant for CF were significantly younger than subjects with IPF or COPD ($P < 0.01$).

Malignancy in the explanted lung

Of the 462 transplant procedures performed, 6 subjects were found to have bronchogenic carcinoma in the explanted lung, resulting in a prevalence of 1.2% (6 out 462 procedures) (Fig. 1, and Fig. 2A-D). All 6 subjects had been diagnosed with interstitial lung disease (ILD), 5 with idiopathic pulmonary fibrosis and one with sarcoidosis (Table 2). This resulted in a prevalence of malignancy of 4.1% (6 of 146) in the ILD population and of 4.2% in those transplanted for pulmonary fibrosis (5 of 117). There was no difference in the mean age of patients with interstitial lung disease who were diagnosed with lung cancer versus the unaffected group ($p > 0.05$). All of these malignancies were identified as adenocarcinomas.

When data were analyzed as before and after the establishment of the LAS system, we found the prevalence of lung cancer in the explanted lung to be 0.38% (one out of 262 patients) in the pre-LAS period and 2.5% (5 out of 200) in the post-LAS period (p Z 0.08).

Lung cancer post-transplant

The prevalence of lung cancer post-lung transplant was 1.9% (9 of 462) (Fig. 1). Bronchogenic carcinoma occurred more frequently in single versus bilateral lung transplant recipients (2.7% versus 0.93% respectively; $p < 0.001$). In subjects transplanted for obstructive lung disease the prevalence was 3.3% (4 of 118 patients with COPD), compared to a prevalence of 2.7% for subjects transplanted for interstitial lung disease (4 of 146 patients with ILD) ($p < 0.05$). However, when comparing to patients who received lung transplant for IPF the prevalence was similar at 3.4% (4 of 117). One subject who was transplanted for CF developed bronchogenic carcinoma.

Of 7 recipients of single lung transplants, carcinoma was detected in the native lung in 5 cases. In one patient with IPF, the disease was metastatic at the time of diagnosis. Cytogenetic studies confirmed the tumor to be recipient derived (male donor in a female recipient). In the other case of a patient with COPD the tumor was metastatic at the time of diagnosis; however it was also confirmed to be recipient related by cytogenetic studies.

Two recipients of bilateral lung transplants developed bronchogenic carcinoma. In one subject with COPD the tumor arose from the right main stem, and was thought to be recipient related. In one subject with cystic fibrosis, the tumor arose from the right hilum. Cytogenetic studies were inconclusive in determining whether the tumor was donor or recipient related.

The time to the discovery of the lung cancer in these 9 subjects ranged from 9 months to 10 years post-transplant, with a mean of 28 months (Table 3).

Of the 9 patients diagnosed with cancer post-transplant the diagnosis was established with a wedge resection/surgical lung biopsy in 6 cases. In 2 cases, bronchoscopy with cytology analysis established the diagnosis and patients were staged with a PET-scan. In one case, cancer was metastatic at the time of diagnosis with diffuse FDG-PET uptake and diagnosis was established with a bone biopsy.

When data were examined in the pre- and post- LAS eras, we found that the prevalence of lung cancer post-transplant to be 1.52% (4 out of 262) in pre LAS, and 2.5% (5 out of 200) in post-LAS ($Z=0.509$).

Changes to the immunosuppressive regimen

When cancer was discovered at the time of transplant, the diagnosis of cancer resulted in a change in the immunosuppressive regimen in all subjects. Mycophenolate mofetil was not introduced or stopped shortly after pathology results. Surveillance biopsies (12 transbronchial biopsies on 6 patients: range 1-4 per subject) did not show any evidence of acute rejection.

When cancer was discovered in post-transplant followup, mycophenolate mofetil was stopped in 5 patients. In 3 patients, the disease was advanced and subjects had elected not to pursue chemotherapy no changes were made to their immunosuppressive regimen.

In all patients tacrolimus levels were kept at the low-end of the desired range according to individual patient years after transplant.

Therapy and outcome

Six patients were diagnosed with lung cancer at the time of transplant, 2 had early stage disease (stage I), and surgery was considered curative. One of these subjects' remains alive at 36 months post-transplant, and the other died 6 months after transplant of sepsis and kidney failure. The remaining 4 subjects had advanced disease with lymph node involvement at the time of surgery; 3 of these subjects received platinum based chemotherapy and one subject declined therapy and passed away within 7 months of transplant. All four patients with advanced disease had evidence of metastasis at the time of their death. The median survival of these 4 patients was 16.5 months (range of 7-25 months).

Nine patients were diagnosed with lung cancer after transplantation, and 4 had early stage disease (stage I). Three patients underwent lung resection for curable disease; one subject remains alive 48 months after resection, one died of unrelated causes 46 months after the cancer diagnosis, and one subject developed recurrent malignancy in the same lung, underwent radiation therapy and died 18 months later from causes directly related to the malignancy. One patient had a lesion potentially curable with surgical resection, however he was suffering from advanced chronic allograft dysfunction and he underwent stereotactic body radiation therapy (SBRT); he remains alive 8 months after the diagnosis. Subjects with stage I lung cancer had a median survival of 32 months (range of 8-48 months).

Five patients had advanced disease (non-stage I) at the time of diagnosis. Four patients died of their malignancy and one patient remains alive 6 months after the diagnosis. Therapy was tailored to the patients' overall functional status and respiratory conditions. Three patients had metastatic disease at the time of diagnosis and elected to receive comfort measures. One subject was found to have extensive disease at the time of surgery, and one subject had advanced disease at the time of diagnosis and underwent chemotherapy and radiation therapy. Both of these subjects remain alive at 8 and 6 months respectively. The median survival of patients with advanced stage lung cancer after transplant was 4 months (range 0.5-7 months).

There was no statistically significant difference in survival comparing subjects diagnosed at the time of transplant to those who were diagnosed in the post-transplant period (Fig. 3A). Since time of diagnosis (at the time of transplant or in post-transplant follow-up) did not result in differences in outcome, we compared all patients diagnosed with stage I lung cancer regardless of time of diagnosis, to patients who had more advanced lung cancer. Subjects with stage I disease had a significantly greater median survival of 27 months (range 6-48 months), as compared to 5 months (range 0.5-25 months) for all other stages (Fig. 3B).

Section 4: Discussion

This study reports on the prevalence of and survival after lung cancer diagnosis in explanted lungs at the time of transplant and on the development of lung cancer post-transplant. We also report outcomes of lung cancer in our patient population and show that patients with limited disease at the time of diagnosis have a significantly better outcome than those with more advanced disease, though still shorter than that of stage I disease in the general population [18]. To our knowledge this is the first study to report on the prevalence and outcome of lung cancer in explanted lungs and post-transplant development of lung cancer in the same population.

At our institution, 1.2% of patients undergoing lung transplantation are found to have lung cancer in their explanted lung despite aggressive screening and surveillance. Our findings are consistent with limited prior reports of lung cancer prevalence in this population. Previous reports have shown a prevalence of 2% [15] and 0.7% [16]. A multinational study of 8000 lung transplants showed that the prevalence of lung cancer in the explanted lung was 0.9%, but this study included a number of patients who received a lung transplant for bronchioloalveolar carcinoma. The prevalence was 0.5% when only patients whose cancer was discovered incidentally in the explanted lungs were included [19]. In this study, patients who did not have any lymph node involvement at the time of transplant had a 51% five-year survival rate, leading the authors to suggest that lung transplant could be a therapy for early stage lung cancer [19]. While the prevalence in our study was similar to other published reports, it represents an under representation of the real prevalence of lung cancer in patients with end-stage lung disease, given that patients with known malignancy are excluded from lung transplantation in our program.

Interestingly, all cases of lung cancer in the explanted lung in our series occurred in patients with

end-stage fibrotic lung disease. Previous reports have shown a higher prevalence of malignancy in patients with obstructive lung disease [15,19]. It is possible that serial yearly CT scans of patients prior to transplant results in easier detection of nodules in patients with COPD than in ILD patients, whose islands of tumor cells may be difficult or impossible to detect radiographically if they are present in areas of fibrosis. The detection of these tumor foci is further complicated by the fact that FDG-PET scans are often positive in fibrotic lung diseases even in the absence of malignancy [20]. It is also likely that the change to LAS based listing in 2005 contributed to this pattern, since patients with fibrotic lung disease have decreased wait-list time and therefore less likely to be diagnosed with a malignancy.

Post-transplant 1.9% of transplant recipients develop de novo bronchogenic carcinoma. Most cases were detected in the native lung of single lung transplant recipients. Although we are limited by the fact that this is a single center cohort, the prevalence we found of post-transplant malignancy is in keeping with the most recent published literature [21,22], and is likely reliable given the aggressive follow-up and screening that is applied to lung transplant recipients. These findings are also consistent with previous reports showing that single lung transplant is associated with higher risk of development of lung cancer [23].

Similar to other reports, despite close follow-up of lung transplant recipients, most lung transplant recipients with lung cancer are diagnosed at a fairly advanced stage [24,25]. Patients with early stage disease had significantly better survival than patients with advanced disease, highlighting the importance of early detection. In our program, post-transplant chest radiographs are obtained at every clinic visit, but CT scans of the chest are performed as clinically indicated. Considering the evidence showing that CT scan screening for lung cancer in high risk groups is an effective strategy to decrease mortality from lung cancer [26], studies investigating the benefits of this strategy in a cohort of lung transplant recipients are needed.

Evidence suggests that immunosuppression is related to an increased incidence of malignancy in solid organ transplant recipients [5]. In line with other studies [24], in our series when lung transplant recipients were diagnosed with lung tumors, their immunosuppressive regimen was modified; most commonly mycophenolate mofetil was stopped. Removing this purine synthesis inhibitor may aid the body launching a more robust antitumor response against the lung cancer

by allowing for greater lymphocyte proliferation. CellCept was often removed in those cases where cancer was progressing more rapidly. There is a paucity of data regarding changes of immunosuppressive regimens in such patients; once cancer is identified in the explanted lung, our data indicates that stopping mycophenolate did not result in an increased incidence of acute allograft rejection. Other investigators have suggested that once a malignancy is diagnosed after transplant, switching immunosuppression to inhibitors of the mammalian target of rapamycin (mTOR) such as sirolimus could be beneficial, with some evidence from the renal transplant literature suggesting a decreased incidence of solid organ malignancy [27,28].

There are a few limitations to our study. First, this is a single center study; second the study was conducted over a long period of time, with changes in standard of care of immunosuppression and cancer care; third, the time to follow-up for some patients is short, with some patients followed for less than 1 year post development of lung cancer.

In conclusion, lung cancer in lung transplant recipients, whether identified in the explants or later in the follow-up period, remains rare. However, outcomes remain poor, with often times advanced stage disease at the time of diagnosis. Survival is better in transplant recipients diagnosed with stage I disease, but was still not comparable to that of the general population in our cohort. Strategies to identify tumors in fibrotic lung disease and in the post-transplant period are needed. The impact of modifying immunosuppressive therapy should be studied in larger cohorts.

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Tables and Figures

Table 1 Characteristics of study population (N = 462).

Age, mean (SD)	49 (13).
Women, n (%)	212 (46)
Bilateral lung transplant, n (%)	214 (46)
Diagnosis n (%)	
-Chronic obstructive pulmonary disease	118 (26).
-Interstitial lung disease	146 (32)
-Idiopathic pulmonary fibrosis	117 (25).
-Pulmonary fibrosis (other causes)	22 (5).
-Sarcoidosis	7 (2).
-Cystic fibrosis	112 (24)
-Primary pulmonary hypertension	19 (4)
Lung cancer n (%)	
-Explanted lung	6 (1.2%)
-Post-transplant	9 (1.9%)

Table 2 Characteristics of subjects diagnosed with lung cancer at the time of transplant.

Patient	Sex	Age	Diagnosis	Smoking (pack-years)	Histology	Stage	Chemotherapy	Status (months)
1	M	49	IPF	25	Adenocarcinoma	T1N1M0	Yes	Deceased (25).
2	F	62	IPF	25	Adenocarcinoma	T1N1M0	No	Deceased (7)
3	M	63	IPF	7	Adenocarcinoma	T2N2M0	Yes	Deceased (25)
4	M	54	PF	–	Adenocarcinoma	T1N0M0	No	Alive (36)
5	M	62	PF	12.5	Adenocarcinoma	T1N0M0	No	Deceased (6)
6	F	54	Sarcoidosis	3	Adenocarcinoma	T1N1M0	Yes	Deceased (8)

IPF: Idiopathic pulmonary fibrosis; PF: pulmonary fibrosis.

Table 3 Characteristics of subjects diagnosed with lung cancer post-transplant.

Age at transplant, sex	Smoking (pack-years)	Time to diagnosis (months)	Type of transplant	Tumor site	Histology	Stage	Therapy	Survival (months)	Status
Idiopathic pulmonary fibrosis									
44, M	–	72	RSLT	Left lung	NSCLC	T1N0M0	Surgery	48	Alive
61, F	40	15	LSLT	Bilateral	NSCLC	T2N2M1	-	0.5	Dead
64, M	25	35	LSLT	Right lung	NSCLC	T1N0M0	SBRT	8	Alive
59, M	60	15	RSLT	Left lung	NSCLC	T4N0M1	Surgery	7	Dead
Chronic obstructive pulmonary disease									
47, M	60	28	LSLT	Right lung	NSCLC	T1N0M0	Surgery	46	Dead
58, F	100	120	RSLT	Left lung	NSCLC	T1N0M0	Surgery[a]	18	Dead
55, F	74	19	LSLT	Left lung	NSCLC	T1N2M1	-	4	Dead
60, M	35	9	Bilateral	Right lung	NSCLC	T4N3M1	-	1	Dead
Cystic fibrosis									
35, M	-	35	Bilateral	Left lung	NSCLC	T2N2M0	C/XRT	6	Alive

LSLT, left single lung transplant; RSLT, right single lung transplant; NSCLC, non-small cell lung cancer; C/XRT: chemotherapy and radiation therapy.

[a] New lesion found in native lung after initial surgery, underwent stereotactic body radiation therapy.

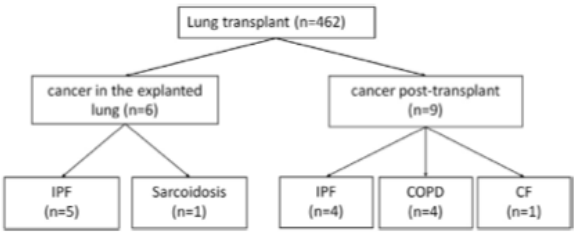

Figure 1 Study flow diagram. (IPF: idiopathic pulmonary fibrosis; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis).

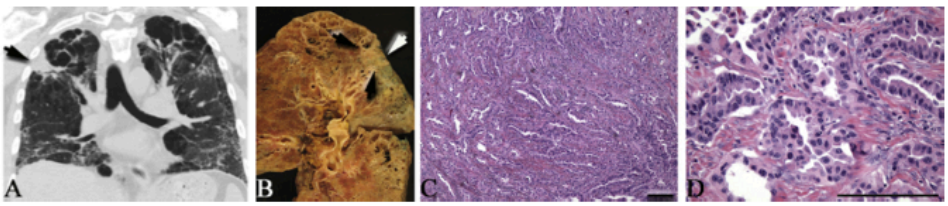

Figure 2 Lung cancer in the explanted lung in a patient with idiopathic pulmonary fibrosis. Computed tomography scan of the chest of a patient with pulmonary fibrosis showing an area of dense consolidation (arrowhead) that had been stable over a 2 year follow-up period (A). Explanted lung showing a mass in the right upper lobe (arrowheads) (B). Low power (C) and high power (D) views of hematoxylin & eosin staining confirm the diagnosis of adenocarcinoma (size bar: 100 μm).

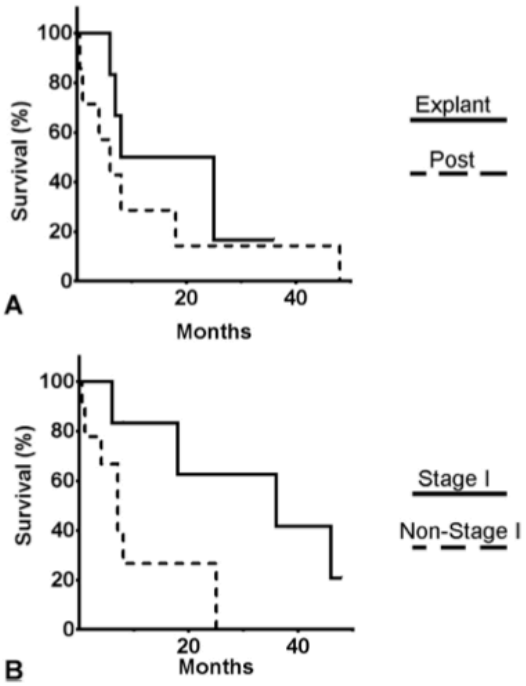

Figure 3 Survival curves of patients with lung cancer. A) Patients with lung cancer diagnosed in the explanted lung (solid line) and in post-transplant (dotted line) ($P > 0.05$). B) Patients with stage I cancer (in explanted lung and post-transplant) (solid line) and patients with other stages (dotted line) ($p < 0.05$).